# Synthesis of 2,4,5-Trisubstituted Oxazoles

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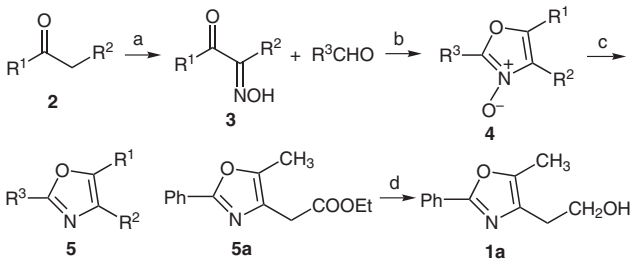
**Abstract:** 2,4,5-Trisubstituted oxazoles were synthesized in good yields starting from α-methylene ketones by nitrosation, condensation with aldehydes and reduction with zinc in acetic acid at 40 °C. (5-Methyl-2-phenyloxazol-4-yl)ethanol was prepared by reduction of ethyl (5-methyl-2-phenyloxazol-4-yl)acetate with $LiAlH_4$.

**Key words:** oxazole, 2,4,5-trisubstituted oxazole, (5-methyl-2-phenyloxazol-4-yl)ethanol, α-diketone monooxime, condensation

Oxazoles have attracted great interest due to their occurrence as subunits of various biologically active natural products and some drug molecules, as well as their applications as valuable precursors in many useful synthetic transformations.[1] (5-Methyl-2-phenyloxazol-4yl)ethanol (**1a**), a 2,4,5-trisubstituted oxazole, is a key intermediate of PPAR agonists for treatment of type 2 diabetes and dyslipidemic,[2] including JTP-20993,[3] muraglitazar,[4] GW409544,[5] GW7845,[6] and some other compounds.[7] However, the present synthetic approaches to **1a** suffer from low yield, more reaction steps, tedious manipulations in the isolation of products and utilization of toxic reagents.[8] Oxazoles are commonly prepared from intermediates such as α-halo ketones,[9] α-diazo ketones,[10] α-acyloxy ketones,[11] and α-acylamino ketones.[12] However, preparations of these reactive intermediates are not always straightforward because of various drawbacks encountered, such as long reaction times, low yields, and forced reaction conditions. Although there are many useful synthetic methods reported for the preparation of substituted oxazoles, practical and convenient methods for the synthesis of 2,4,5-trisubstituted oxazoles have been quite limited.[13,14] Therefore, development of a more convenient and efficient method for the synthesis of multisubstituted oxazoles is of prime necessity.

Here we describe a simple procedure for the synthesis of 2,4,5-trisubstituted oxazole **5** in higher yields (Table 1) by reduction of unstable intermediate **4** with zinc or catalytic hydrogenation. The *N*-oxides **4** could be obtained by condensation of aldehyde and α-diketone monooxime **3** in acetic acid saturated by dry HCl gas (Scheme 1). Intermediates **3** could easily be prepared by treating α-methylene ketones **2** with methyl nitrite in diethyl ether saturated by dry HCl gas at room temperature.




**Scheme 1** *Reagents and conditions*: a) MeONO, dry HCl, $Et_2O$, r.t.; b) dry HCl, AcOH; c) AcOH, Zn, 40 °C, 0.5 h or Pd/C, $H_2$, MeOH, r.t.; d) $Et_2O$, $LiAlH_4$, 93%.

**Table 1** Synthesis of α-Diketone Monooximes **3** and 2,4,5-Trisubstituted Oxazoles **5**

| $R^1$ | $R^2$ | $R^3$ | Products | Yields (%)[a] |
|---|---|---|---|---|
| Me | $CH_2CO_2Et$ | Ph | **3a**, **5a** | 80, 76 |
| Me | Me | Ph | **3b**, **5b** | 83, 85 |
| Me | $COCH_3$ | Ph | **3c**, **5c** | 74, 88 |
| Ph | Me | Ph | **3d**, **5d** | 74, 81 |
| Me | $CO_2Et$ | Ph | **3e**, **5e** | 78, 90 |
| Me | $CO_2Et$ | 2-furyl | **3e**, **5f** | –, 84 |
| Me | $CO_2Et$ | *i*-Pr | **3e**, **5g** | –, 93 |

[a] Isolated yields.

In conclusion, a simple and attractive procedure for the synthesis of 2,4,5-trisubstituted oxazoles was developed in good yields. This procedure is effective, including easy work-up, shorter reaction time, higher yield and avoidance of hazardous reagents.

All starting compounds were used as received from commercial sources without further purification. Melting points were determined on XRC-1 micromelting point apparatus and are uncorrected. Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co. Ltd.). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker Avance 600 spectrometer with TMS as internal standard. ESI-MS and IR spectra were obtained on a Finnigan $LCQ^{DECA}$ and a Perkin-Elmer spectrum one FT-IR spectrometer (KBr disc), respectively.

**α-Diketone Monooximes 3a–e; General Procedure**

Methyl nitrite (2.95 g, 45 mmol) was bubbled through a solution of an appropriate α-methylene ketone **2** (30 mmol) in $Et_2O$ (40 mL)

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saturated with dry HCl gas at r.t. The reaction mixture was stirred for 2 h. After completion of the reaction (monitored by TLC), $H_2O$ (50 mL) was added, the organic layer was separated, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with $H_2O$ and brine, and dried ($Na_2SO_4$). After concentration, the residue was purified by silica gel column chromatography [petroleum ether (bp 60–90 °C)–EtOAc, 12: 1] to give **3a**, or recrystallized from toluene, for **3b–e** (Table 1).

**Ethyl 3-Hydroxyimino-4-oxopentanoate (3a)**
Yield: 4.15 g (80%) (Lit.[15] yield: 60%); yellow oil.

IR (KBr): 3338, 2987, 2922, 2874, 1739, 1694, 1629, 1438, 1369, 1344, 1179, 1106, 1003 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 1.90 (br s, 1 H), 2.10 (s, 2 H), 2.25 (s, 3 H), 4.14 (q, *J* = 7.1 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 14.2, 21.8, 32.2, 59.7, 164.3, 166.5, 197.7.

ESI-MS: *m*/*z* (%) = 196 ([M + $Na^+$], 72), 173 ([$M^+$], 13), 158 ([M – $CH_3$]$^+$, 16), 144 ([M –$CH_2CH_3$]$^+$, 30).

**3-Hydroxyiminobutan-2-one (3b)**
Yield: 2.51 g (83%); colorless crystals; mp 74–75 °C (Lit.[15] mp 75–76 °C).

**3-Hydroxyiminopentane-2,5-dione (3c)**
Yield: 2.86 g (74%); colorless crystals; mp 69–70 °C (Lit.[16] mp 72–73 °C).

**2-Hydroxyimino-1-phenylpropanone (3d)**
Yield: 3.61 g (74%); colorless crystals; mp 112–113 °C (Lit.[17] mp 113–115 °C).

**Ethyl 2-Hydroxyimino-3-oxobutyrate (3e)**
Yield: 3.72 g (78%); white crystals; mp 57–58 °C.

IR (KBr): 3324, 2972, 2942, 2874, 1736, 1676, 1629, 1373, 1317, 1254, 1157, 1076, 958, 857, 723 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.33 (t, *J* = 7.0 Hz, 3 H), 1.92 (br s, 1 H), 2.28 (s, 3 H), 4.15 (q, *J* = 7.0 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 14.0, 21.6, 60.3, 162.5, 163.4, 198.2.

ESI-MS: *m*/*z* (%) = 158 ([M – H]$^-$, 65), 159 ([$M^-$], 5).

**Oxazoles 5a–g; General Procedure**
A solution of α-diketone monooxime **3** (3 mmol) and the corresponding aldehyde (3.3 mmol) in AcOH (15 mL) was cooled to 0–5 °C, and dry HCl gas was bubbled through the reaction mixture for 0.5 h. The mixture was stirred at the same temperature for 2 h and was diluted with $Et_2O$ (45 mL). The white solid intermediate **4** was filtered and washed with $Et_2O$ (10 mL). It was then dissolved in AcOH (5 mL), and zinc (0.390 g, 6 mmol) was added. The mixture was stirred at 40 °C for 0.5 h, and $H_2O$ (40 mL) was added to the mixture. The mixture was extracted with $Et_2O$, and the organic layer was washed with $H_2O$ and brine, and dried ($Na_2SO_4$). The solvent was removed to give **5** (Table 1).

**Ethyl (5-Methyl-2-phenyloxazol-4-yl)acetate (5a)**
Yield: 0.559 g (76%); yellow oil.

IR (KBr): 3063, 2983, 2926, 1739, 1643, 1555, 1488, 1449, 1370, 1204, 1161, 1027, 878, 776, 692 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 2.38 (s, 3 H), 3.57 (s, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 7.40–7.45 (m, 3 H), 7.99 (dd, *J* = 8.1, 1.5 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 12.5, 14.4, 28.7, 60.2, 125.3, 128.5, 129.2, 130.4, 156.4, 159.6, 163.2.

ESI-MS: *m*/*z* (%) = 268 ([M + $Na^+$], 100), 273 ([M + $K^+$], 41), 246 ([M + H]$^+$,19), 172 ([M – $CH_2CO_2Et$]$^+$, 24).

*Alternative Method for **5a***: A solution of **3a** (1.73 g, 10 mmol) and benzaldehyde (1.16 g, 11 mmol) in AcOH (15 mL) was cooled to 0–5 °C, and dry HCl gas was bubbled into the reaction mixture for 1 h. The mixture was stirred at r.t. for 2 h and then diluted with $Et_2O$ (40 mL). The white solid was filtered, washed with $Et_2O$ (10 mL) and then dissolved in MeOH (15 mL). The mixture was hydrogenated with 5% Pd/C (0.14 g) under atmospheric pressure at r.t. for 4 h. The catalyst was filtered off and washed with a small amount of MeOH. The combined filtrates were concentrated in vacuo to yield **5a**; yield: 1.76 g (72%); yellow oil.

**4,5-Dimethyl-2-phenyloxazole (5b)**
Yield: 0.441 g (85%); white solid; mp 43–45 °C.

IR (KBr): 3059, 2924, 1642, 1612, 1553, 1488, 1449, 1339, 1240, 1153, 1068, 948, 754, 774, 711, 691 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.17 (s, 3 H), 2.30 (s, 3 H), 7.40–7.45 (m, 3 H), 7.99 (dd, *J* = 8.3 Hz, 1.5 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 10.1, 11.3, 125.8, 127.8, 128.7, 129.6, 131.9, 143.4, 159.1.

ESI-MS: *m*/*z* (%) = 212 ([M + $K^+$], 8), 174 ([M + H]$^+$, 100).

**4-Acetyl-5-methyl-2-phenyloxazole (5c)**
Yield: 0.531 g (88%); white solid, mp 71–73 °C.

IR (KBr): 3055, 3002, 2933, 1684, 1596, 1483, 1450, 1380, 1355, 1195, 1074, 955, 934, 778, 713, 690 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.61 (s, 3 H), 2.70 (s, 3 H), 7.46–7.48 (m, 3 H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 12.4, 27.9, 126.4, 126.9, 128.8, 130.6, 135.8, 154.5, 158.7, 195.4.

ESI-MS: *m*/*z* = 202 ([M + H]$^+$, 70%).

**4-Methyl-2,5-diphenyloxazole (5d)**
Yield: 0.572 g (81%); white solid; mp 75–77 °C.

IR (KBr): 3053, 2930, 1685, 1615, 1552, 1472, 1435, 1354, 1245, 1074, 1014, 955, 912, 772, 712, 690 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.51 (s, 3 H), 7.33–7.35 (m, 1 H), 7.45–7.49 (m, 5 H), 7.70 (dd, *J* = 7.9 Hz, 2 H), 8.09 (d, *J* = 7.3 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 13.5, 125.4, 126.2, 127.4, 127.7, 128.7, 128.9, 129.2, 130.2, 133.4, 145.5, 159.4.

ESI-MS: *m*/*z* = 236 ([M + H]$^+$, 100%).

**Ethyl (5-Methyl-2-phenyloxazol-4-yl)carboxylate (5e)**
Yield: 0.624 g (90%); colorless oil.

IR (KBr): 3050, 2977, 2875, 1715, 1615, 1563, 1449, 1372, 1342, 1237, 1186, 1105, 1057, 786, 710, 691 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.43 (t, *J* = 7.1 Hz, 3 H), 2.73 (s, 3 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 7.46–7.48 (m, 3 H), 8.08 (dd, *J* = 7.7, 1.6 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 12.3, 14.4, 60.1, 126.6, 128.7, 128.9, 130.7, 156.2, 159.7, 162.5.

ESI-MS: *m*/*z* (%) = 270 ([M + $K^+$], 15), 254 ([M + $Na^+$], 100), 232 ([M + H]$^+$, 3).

**Ethyl (2-Furyl-5-methyloxazol-4-yl)carboxylate (5f)**
Yield: 0.557 g (84%); yellow solid; mp 80–82 °C.

IR (KBr): 3144, 3121, 2984, 2931, 1731, 1643, 1628, 1599, 1547, 1478, 1390, 1376, 1307, 1225, 1190, 1126, 1018, 953, 885, 787, 724 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.41 (t, *J* = 7.0 Hz, 3 H), 2.70 (s, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 6.54 (m, *J* = 1.5 Hz, 1 H), 7.10 (d, *J* = 3.42 Hz, 1 H), 7.58 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 12.1, 14.4, 61.1, 111.9, 112.3, 128.6, 142.1, 144.7, 152.3, 155.7, 162.2.

ESI-MS: *m*/*z* (%) = 260 ([M + $K^+$], 19), 244 ([M + $Na^+$], 100), 222 ([M + H]$^+$, 3).

**Ethyl (2-Isopropyl-5-methyloxazol-4-yl)carboxylate (5g)**
Yield: 0.505 g (93%); yellow oil.

IR (KBr): 2970, 2875, 2823, 1712, 1610, 1540, 1472, 1350, 1230, 1177, 1105, 1059, 1010, 792, 728, 693 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.34 (d, *J* = 7.0 Hz, 6 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 2.60 (s, 3 H), 3.10 (m, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 12.0, 14.4, 20.3, 28.4, 60.8, 127.1, 155.8, 162.6, 166.9.

ESI-MS: *m*/*z* (%) = 236 ([M + $K^+$], 7), 220 ([M + $Na^+$], 26), 198 ([M + H]$^+$, 100).

**(5-Methyl-2-phenyloxazol-4-yl)ethanol (1a)**
A solution of **5a** (1.23 g, 5 mmol) in $Et_2O$ (30 mL) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (0.185 g, 5 mmol) in $Et_2O$ (100 mL). The mixture was stirred at r.t. for 1 h, cooled in an ice bath, and aq 2 M HCl (15 mL) was added dropwise. The organic layer was separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were washed with brine, dried ($Na_2SO_4$). The solvent was removed in vacuo to afford **1a**; yield: 0.943 g (93%); white powder; mp 72–73 °C (Lit.[8e] mp 73–74 °C).

IR (KBr): 3304, 3059, 2942, 2901, 2872, 1647, 1555, 1486, 1428, 1338, 1222, 1133, 1053, 777, 721, 691 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.36 (s, 3 H), 2.75 (t, *J* = 5.9 Hz, 2 H), 3.20 (br s, 1 H), 3.95 (t, J = 5.8 Hz, 2 H), 7.42–7.46 (m, 3 H), 7.98 (dd, *J* = 8.1, 1.5 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 10.1, 28.0, 61.9, 125.9, 127.5, 128.7, 130.0, 134.9, 144.1, 159.6.

ESI-MS: *m*/*z* (%) = 226 ([M + $Na^+$], 32), 204 ([M + H]$^+$, 100), 186 ([M – OH]$^+$, 26).

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